
Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis.

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Public Summary:

Scientific Abstract:

Metastatic progression depends on genetic alterations intrinsic to cancer cells as well as the inflammatory microenvironment of advanced tumours. To understand how cancer cells affect the inflammatory microenvironment, we conducted a biochemical screen for macrophage-activating factors secreted by metastatic carcinomas. Here we show that, among the cell lines screened, Lewis lung carcinoma (LLC) were the most potent macrophage activators leading to production of interleukin-6 (IL-6) and tumour-necrosis factor-alpha (TNF-alpha) through activation of the Toll-like receptor (TLR) family members TLR2 and TLR6. Both TNF-alpha and TLR2 were found to be required for LLC metastasis. Biochemical purification of LLC-conditioned medium (LCM) led to identification of the extracellular matrix proteoglycan versican, which is upregulated in many human tumours including lung cancer, as a macrophage activator that acts through TLR2 and its co-receptors TLR6 and CD14. By activating TLR2:TLR6 complexes and inducing TNF-alpha secretion by myeloid cells, versican strongly enhances LLC metastatic growth. These results explain how advanced cancer cells usurp components of the host innate immune system, including bone-marrow-derived myeloid progenitors, to generate an inflammatory microenvironment hospitable for metastatic growth.

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